Initially, the Office comments that it would like to consider co-pending applications, but is unable to obtain access to the files. The applicants provide the claims pending in application Serial No. 09/913,772 (Our Ref: PF 94 PCT SEQ), and Serial No. 09/913,107 (Our Ref: PF 91 PCT SEQ). The applicants submit that the instant claims, as presently amended do not read on the referenced disclosures.

The Draftsperson issued a Drawings Objection. The applicants supply replacement drawings which respond to the objections of the Draftsperson.

The Office objects to the format of the Specification. The applicants acknowledge the Office's objection as to the Specification format and comment that we will, in future, strive to conform with this non-mandatory requirement. Moreover, the applicants acknowledge the Office notation that the Specification makes reference to substances which are identified by their registered trademarks. The applicants will, in future, strive to conform with this non-mandatory requirement.

The applicants have completed the italicization of *Klebsiella pneumoniae* in Claim 31.

Substantively, the claims of the instant application are rejected for a variety of written description and enablement issues under 35 USC § 112, first paragraph; a variety of indefiniteness issues under 35 USC § 112, second paragraph; and lack of novelty rejections under 35 USC § 102 in view of two PIERRE FABRE MÉDICAMENT published International Applications.

All claims are rejected under 35 USC § 112, first paragraph, for not complying with the written description requirement. The rejection is directed to the language of Claim 32 drawn to an OmpA protein fragment having at least 80% homology with the sequence of SEQ ID 2. The applicants cancel this claim with the instant Response and Amendment.

Similarly, the rejection of all claims under 35 USC § 112, first paragraph, for lack of enablement because the Specification does not enable the process of using an OmpA protein fragment having at least 80% homology with the sequence of SEQ ID 2, or a fragment having at least 5 amino acids corresponding to the disclosed sequence, in the preparation of a composition of the instant invention, is hereby obviated by the amendment to the instant claims.

Under 35 USC § 112, second paragraph, various claims are rejected for various indefiniteness issues. The rejections and responses thereto are as follows:

a) Claims 25, 26, 29, 30, 32, 34, 36 and 38 do not define fragment. The language is no longer present in the claims as instantly amended.

b) Claim 29 is rejected for failing to define the steps for obtaining the instant composition through culture and extraction. Claim 29 has been canceled.

c) Generic Claim 25 is rejected for failing to define the steps of the process for preparing the composition of the invention. It is submitted that the instant amendment defines the "method" of the instant invention.

d) The applicants are requested to identify whether "enterobacterium" refers to a genus or family in Claims 25, 26 and 29-31. The term has been removed from the amended claims.

e) The applicants are requested to identify whether "it" in Claim 25 is directed to the OmpA protein, the biologically active substance, or otherwise. It is submitted that the instant amendment obviates the rejection.

f) The applicants are requested to identify whether in Claim 26, the specific binding of the protein or fragment is part of the claimed invention. Claim 26 is canceled with the instant amendment.

g) The applicants are asked to rephrase the language of Claim 32. Claim 32 has been canceled.

h) The applicants are asked to rephrase the language of Claim 32. Claim 32 has been canceled.

i) The applicants are asked to correct the article "a" in Claim 32. Claim 32 has been canceled.

* * * * *

Finally, and most significantly, all claims are rejected for lack of novelty under 35 USC § 102(a) in view the printed publication before invention of Andreoni, et al. WO 99/49892 and under 35 USC § 102(b) in view of the printed publication more than one year before invention of Binz, et al. WO 97/41888.

With regard to the rejection based on the Andreoni, et al. disclosure, it is the position of the Office that the prior international publication discloses a process of using an enterobacterial outer membrane protein A fragment to improve immunity to an antigen or hapten. It is submitted that Andreoni, et al. disclose a biological RSV antigen covalently coupled to the P40 OmpA protein for preparing a pharmaceutical composition which is intended to be administered intra-nasally. P40 is used as a protein carrier for an antigen in order to increase the immune response against the coupled antigen.

In contrast to the instant invention, Andreoni, et al. do not disclose, nor suggest, that the P40 OmpA protein is capable of specifically binding to antigen-presenting cells (APC) and to be internalized by these APC's together with the active substance coupled with P40. Thus, it is submitted that the Office has not identified a *prima facie* basis for an anticipation rejection. Reconsideration and withdrawal are respectfully solicited.

With regard to the rejection based on the Binz, et al. disclosure, it is the position of the Office that the international publication of Binz, et al., more than one year before the filing date of the instant application, discloses an amino acid sequence which is a truncated version of the instant SEQ ID NO. 2. Moreover, it is the position of the Office that the prior art compositions are intended for presentation targeting of the biologically active substance to host antigen-presenting cells, such as dendritic cells, macrophages or B lymphocytes.

The applicants acknowledge that Binz, et al. disclose oligosaccharidic antigens coupled to the P40 OmpA protein and the use of this P40 OmpA protein as a protein carrier of oligosaccharides for improving the immune response against an oligosaccharadic antigen in a mammal. This reference does not, however,

disclose nor suggest that P40 OmpA is capable of binding to an APC and to be internalized into the APC with the coupled active substance.

Thus, neither cited reference discloses nor suggests a method to specifically deliver an active substance into APC's by coupling the active substance with the P40 OmpA protein, as claimed in the instant invention.

Moreover, and in contrast to the Office's conclusion that it is inherent from the disclosure of Binz, et al. that the Binz, et al. composition is intended for specific presentation of active substance (antigen) to the host APC's, the applicants assert that the present inventors have demonstrated in Example 6 (see Figure 4 at page 19 of the Specification) that other carrier proteins, such as TT or BB, which are currently used for increasing immune response against antigens coupled thereto, are not capable of binding to APC's and thus not internalized by APC's. Therefore, the capability of a carrier to enhance an immune response to an associated antigen is not inherent in its capacity to bind APC's or to be internalized within these cells.

Therefore, one skilled in the art would not have concluded from the disclosure of the referenced applications that it would have been obvious at the time of the present invention that P40 OmpA protein is capable of binding APC's and to be internalized into APC's with the coupled active substance and consequently to use the coupled substance with P40 for specifically *in vitro* or *in vivo* delivery of that substance into the APC's according to the present invention.

* * * * *

Accordingly, entry of the present amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited. Moreover, the applicants take this opportunity to supply the office with copies of the references cited in the International Search Report (which should have already been supplied by the Receiving Office) and the references cited in the specification. Entry of the attached Form PTO-1449 into the record of the application is respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: _____
G. PATRICK SAGE

Dated: December 1, 2003
Customer No.: 25,666
500 Columbia Plaza
350 East Michigan Ave.
Kalamazoo, MI 49007-3856
(269) 382-0030

Enclosure: Listing of Claims,

Listing of Claims for Serial No. 09/913,772 (Our Ref: PF 94 PCT SEQ),

Listing of Claims for Serial No. 09/913,107 (Our Ref: PF 91 PCT SEQ),

Replacement Drawings,

Form PTO-1449 and accompanying references, and

Postal Card Receipt

* * * * *

THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR DEFECT IN THE ATTACHED CHECK, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.

LISTING OF CLAIMS

25. (Presently Amended) ~~A process of using an enterobacterium OmpA protein, or a fragment thereof, for preparing a composition intended for specific targeting of a biologically active substance, which is associated with it, to antigen-presenting cells, wherein said enterobacterium OmpA protein, or fragment thereof, is internalized into the antigen presenting cells.~~ A method for delivering a biologically active substance to antigen-presenting cells comprising the step of:

a) covalently coupling said active substance to the OmpA protein of *Klebsiella pneumoniae* having the amino acid sequence of SEQ ID No. 2; and

b) contacting said coupled active substance obtained in step a) with said antigen-presenting cells.

26. (Canceled)

27. (Presently Amended) The ~~process~~ method of claim 25, wherein said antigen-presenting cells are chosen from dendritic cells, monocytes and B lymphocytes.

28. (Presently Amended) The ~~process~~ method of claim 27, wherein said antigen-presenting cells are dendritic cells.

29. (Canceled)

30. (Canceled)

31. (Presently Amended) The ~~process~~ method of claim 25, wherein said OmpA protein of ~~enterobacterium is Klebsiella~~ *Klebsiella pneumoniae* is a recombinant protein.

32. (Canceled)

33. (Canceled)

34. (Canceled)

35. (Presently Amended) The ~~process~~ method of claim 25 ~~34~~, wherein the covalent coupling ~~by covalent attachment~~ is chemical coupling.

36. (Presently Amended) The ~~process~~ method of claim 35, wherein one or more attachment elements are introduced into said OmpA protein of *Klebsiella pneumoniae*, ~~or a fragment thereof, and/or into said biologically active substance,~~ in order to facilitate the chemical coupling.

37. (Presently Amended) The ~~process~~ method of claim 36, wherein said attachment element ~~introduced~~ is an amino acid.

38. (Presently Amended) The ~~process~~ method of claim 25 ~~34~~, wherein said ~~biologically~~ active substance ~~coupled by covalent attachment~~ covalently coupled with said OmpA protein~~, or a fragment thereof,~~ is a recombinant chimeric protein resulting from the expression of a nucleic acid construct encoding said ~~biologically~~ active substance and said OmpA protein~~, or a fragment thereof~~.

39. (Presently Amended) The ~~process~~ method of claim 25 ~~38~~, wherein said ~~biologically~~ active substance is an antigen or a hapten.

40. (Withdrawn) A method for modifying the immune response to an antigen or a hapten with a composition intended for specific targeting of a biologically active substance, which is associated with it, to antigen-presenting cells, wherein an enterobacterium OmpA protein, or a fragment thereof, is internalized into the antigen-presenting cells.

41. (Withdrawn) The method of claim 40 for improving the immune response to an antigen or a hapten.

42. (Withdrawn) The method of claim 40 for preventing or treating a disease.

43. (Withdrawn) The method of claim 42, for preventing or treating a disease with an active substance, the effectiveness of which is modified by and/or linked to the internalization thereof by dendritic cells.

44. (Withdrawn) The method of claim 43, for preventing or treating cancers, preferably cancers associated with a tumor antigen, autoimmune diseases, allergies, graft rejections, cardiovascular diseases, diseases of the central nervous system, inflammatory diseases, infectious diseases or diseases linked to an immunodeficiency.

45. (Withdrawn) The method of claim 44, for preventing or treating an infectious disease or a cancer associated with a tumor antigen.

46. (Withdrawn) A pharmaceutical composition effective in the method of claim 42 which comprises an adjuvant of immunity.

47. (Withdrawn) The pharmaceutical composition of claim 46 which is vehicled in a form which makes it possible to improve the stability and/or immunogenicity thereof.

48. (Withdrawn) The pharmaceutical composition of claim 46 which is vehicled in the form of a liposome, of a viral vector, or of a transformed

host cell capable of expressing a recombinant chimeric protein resulting from the expression of a nucleic acid construct encoding said biologically active substance and said OmpA protein, or a fragment thereof.